REMARKS/ARGUMENTS

Claims 1-34 are pending in this application. Claims 1-11, 13 and 16 have been cancelled. The Office Action mailed on December 24, 2009 includes the following rejections:

1. Claims 17-18, 20 and 24 are rejected under 35 U.S.C. § 112, first paragraph, enablement.
2. Claims 12, 14, 18-22, 24-27, and 29-34 are rejected under 35 U.S.C. § 103(a) as being unpatentable by the combination of Hall-Jackson and Sweatt.
3. Claims 15, 17, and 23 are rejected under 35 U.S.C. § 103(a), as being unpatentable by the combination of Hall-Jackson, Sweatt and Varga.

Statement of Joint Inventorship.

Applicants were advised in the prior and in this Office Action of the obligation under 37 C.F.R. 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the Examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a). Applicants hereby re-state, as was stated in the last response (Amendment 8/28/09, page 8), that the assignment rights for each inventor were commonly owned by the assignee at the time of each invention as claimed pursuant to 37 C.F.R. § 1.56.

Claim Rejections – Claims 17-18, 20 and 24 remain rejected under 35 U.S.C. § 112, first paragraph, enablement.

Applicants respectfully submit that the present application is enabled to support claims 12, 14, 17-18, 20, 22-27 and fully complies with 35 U.S.C. § 112, first paragraph. Applicants traverse the rejection, however, solely to move prosecution forward Applicants have amended the claims; no equivalents are disclaimed by this amendment. Applicants respectfully request the Examiner withdraw the rejection under 35 U.S.C. § 112, first paragraph.

Claim Rejections – Claims 12, 14, 18-22, and 24-27 are rejected under 35 U.S.C. § 103(a) as being unpatentable over U.S. Publication No. 2002/0058699 to Sweatt, et al. (hereinafter Sweatt) and Hall-Jackson, et al., in Paradoxical Activation of Raf by a Novel Raf Inhibitor, Chemistry & Biology, August 1999, Vol. 6 pp. 559-568 (hereinafter Hall-Jackson).

Neurodegenerative diseases are a subset of neurological diseases characterized by an abnormal loss of neurons. Epilepsy is a neurological disease but not a neurodegenerative disease because epilepsy does not directly cause neuronal loss. The defining feature of epilepsy is excessive brain neuronal excitability (not neuronal loss).

The Action cites to Roux, "p75 Neurotropin Receptor Expression is Induced in Apoptotic Neurons after Seizure," J. of Neuroscience, Vol 19 (16), pp. 6887-686, as evidence that epilepsy and seizures associated therewith cause neuronal cell loss. Roux is alleged to stand for the proposition that "seizures causes [sic] neuronal cell loss in both animal model and human epilepsy. Therefore, seizures do in fact cause neuronal cell loss as demonstrated by Roux." (page 3).

In rebuttal to that position, and therefore the central basis for the argument of obviousness, please find the letter of Rajiv. R. Ratan, M.D., Ph.D., Burke Professor of Neurology and Neuroscience at Weill Medical College and Executive Director of the Burke-Cornell Medical Research Institute (Exhibit A and Dr. Ratan's Resume, Exhibit B). Dr. Ratan is an expert in the field of acute and chronic neurodegenerative conditions and states unequivocally that epilepsy, "is not considered a neurodegenerative disorder" because epilepsy "is not associated with a chronic deteriorating clinical course or any histopathological evidence or progressive neurodegeneration."

Further support for the lack of any connection between epilepsy and neuronal cell death is found in Exhibit C, a printout from the website of the National Institutes of Health, National Institute of Neurological Disorders and Stroke (NINDS) website. On page 3, under the title, "What Causes Epilepsy", the NINDS website states:

> Epilepsy may develop because of an abnormality in brain wiring, an imbalance of nerve signaling chemicals called *neurotransmitters*, or some combination of these factors. Researchers believe that some people with epilepsy have an abnormally high level of *excitatory neurotransmitters* that increase neuronal activity, while others have an abnormally low level of *inhibitory neurotransmitters* that decrease neuronal activity in

> the brain. Either situation can result in too much neuronal activity and cause epilepsy. One of the most-studied neurotransmitters that plays a role in epilepsy is *GABA*, or gamma-aminobutyric acid, which is an inhibitory neurotransmitter. Research on GABA has led to drugs that alter the amount of this neurotransmitter in the brain or change how the brain responds to it. Researchers also are studying excitatory neurotransmitters such as glutamate. (emphasis in original).

Nothing in the official website of the NINDS regarding epilepsy teaches that it is a neurodegenerative disease. Furthermore, a world expert on epilepsy states that same. Therefore, the *prima facie* case of obviousness fails because the skilled artisan would not be compelled to equate epilepsy with neuronal cell death and would, therefore, not look to the teachings of Sweatt to extend from seizures to cell death.

Sweatt specifically states that, "a seizure represents a discrete, abnormal episode of hyperexcitability in brain structures, influencing motor or sensory function, behavior, or consciousness", (Sweatt [0003]). In contrast, neurodegenerative diseases are a subset of neurological diseases characterized by an abnormal loss of neurons. As demonstrated hereinabove, epilepsy **does not** cause neuronal loss. While epilepsy is a neurological disease, it is **not** a neurodegenerative disease. The defining feature of epilepsy is excessive brain neuronal excitability (not neuronal loss)(Sweatt [0003]). Therefore, the skilled artisan would not be motivated to look to Sweatt for how to treat a neurodegenerative disease, when on its face, Sweatt is directed to the use of compounds to treat the hyperexcitability associated with seizures.

In contrast, the present invention uses a different c-Raf inhibitor than Sweatt to treat a different class of neurological disorders, specifically neurodegenerative disorders, of which epilepsy/seizure is not part of (as found in the teachings of Sweatt). Excessive neuronal excitability is not a feature of neurodegenerative diseases and as such is not relevant to the claimed invention. On the contrary, patients with neurodegenerative diseases generally display sharply reduced brain neuronal activity. Therefore, there is no motivation to follow the teachings of Sweatt in combination with any other reference related to c-Raf inhibitors.

Hall-Jackson teaches that, when transformed cells are treated with c-Raf/B-Raf inhibitors such as ZM336372, a paradoxical activation of c-Raf results. Hall-Jackson concludes, **"compounds which inhibit the kinase activity of Raf may not be useful as anticancer drugs"** (Conclusions, page 559). Hall-Jackson does not address the issue of neurological or a neurodegenerative disease in their paper and the present invention is not directed to the use of

Raf inhibitors for the treatment of cancer. In contrast, the claims of the present invention are directed to a method of reducing neuronal cell death in a mammal suffering from or susceptible to neurodegenerative disease, cerebral ischaemia, traumatic neuronal injury, paralysis, or spinal cord injury, comprising administering to the mammal an effective amount of a 3-substituted indolones that is a C-Raf inhibitor or a pharmaceutically acceptable salt–thereof sufficient to reduce neuronal cell death. Hall-Jackson also fails to teach at least one element or limitation of the claimed invention, namely, any teaching of administering an effective amount of the 3-substituted indolones to reduce a neurodegenerative disease. The only disease mentioned by Hall-Jackson is cancer, and the purpose of their study is to eliminate the cancer cells, not prevent their death. They found that their compound failed to prevent the activity of the c-Raf protooncogene because of a feedback mechanism between the c-Raf and B-raf isoforms. In fact, the only cell data provided by Hall-Jackson teaches that the compound had no effect on the treated cells (Table 2).

Specifically, Hall-Jackson states the following about the compounds effect on cells:

> **shown). Consistent with these observations, and unlike PD 98059 [23], ZM 336372 (10 μM) also failed to inhibit the constitutive activation of p44 MAPK or p42 MAPK seen in the human colon tumour cell line HCT116 (Figure 4) and H-ras transformed NIH3T3 cells (data not shown) and did not affect either the proliferation or morphology of NIH3T3 cells transformed by either overexpression of H-ras or constitutively activated c-Raf (Table 2). Moreover, unlike PD 98059, ZM 336372 was** (Hall-Jackson, page 562).

Therefore, not only does Hall-Jackson not address the issue of neurological or neurodegenerative diseases, nor the amounts need to have an effective amount of the compound for the prevention on cell death, all that Hall-Jackson teaches is that the compounds "did not effect the proliferation or morphology of NIH3T3 cells transformed by either overexpression of H-ras or constitutively activated c-Raf." (page 562). Therefore, there would be no motivation to combine the teachings of Hall-Jackson (that is has no effect on cells) with the Roux reference or Sweatt. The skilled artisan would understand from reading Hall-Jackson and combining it with Sweatt that raf inhibitors are ineffectual on cells, and would not use them, alone or in combination with Sweatt, because they are not useful for the purpose argued in the Office Action.

As regards the Office's position that "any individual is susceptible to neurodegenerative disease as the individual ages and would benefit by the administration of c-Raf inhibitors" (page 8), Applicants fail to see the relevance or purpose for the inclusion of this statement in the Action.

Finally, the Action states, as best understood by Applicants' counsel, that the c-raf inhibitor would have the same effect as over-expression of c-Raf and that it would inhibit cell death via B-raf regulation (page 8). If the Office has a specific scientific citation to support this proposition and an argument for a rejection, Applicants will be glad to address such art when presented, and a rejection when it is made based on that art.

Accordingly, claims 12, 14, 18-22, and 24-27 are not rendered obvious from the combination of Sweatt and Hall-Jackson and/or Roux. Applicant respectfully requests the Examiner withdraw the rejection under 35 U.S.C. § 103(a).

Claim Rejections – Claims 15, 17 and 23 are rejected under 35 U.S.C. § 103(a), as being unpatentable over Sweatt, et al., in U.S. Publication No. 2002/0058699 (hereinafter Sweatt) and Hall-Jackson, et al., in Paradoxical Activation of Raf by a Novel Raf Inhibitor, Chemistry & Biology, August 1999, Vol. 6 pp. 559-568 (hereinafter Hall-Jackson), and further in view of Varga, Eur. J. of Pharmacol. 451, 2002, pp. 101-102.

Applicants traverse the rejection and incorporate herein by reference their arguments against Sweatt and Hall-Jackson made hereinabove.

Varga is added to provide a teaching that in cultured cells GW5074 reduces the overactivation of adenyl cyclase in response to treatment with synthetic opioid. This finding has no bearing whatsoever on neurodegeneration or the use of GW5074 as a therapeutic drug for treating neurodegenerative diseases. First, the Varga reference does not refer to any neurological or neurodegenerative diseases; as such, the skilled artisan would have not motivation to attempt to use it for the treatment of neurodegeneration. At most, Varga suggests that GW5074 could have value in treating opioid addiction. That GW5074 reduces the overactivation of adenyl cyclase in response to treatment with synthetic opioid, has no bearing whatsoever on neurodegeneration or the use of the c-Raf inhibition as a therapeutic drug for treating

neurodegenerative diseases. Nothing in Sweatt or Hall-Jackson helps overcome this deficiency in Varga because, as argued hereinabove, they fail to support a *prima facie* case of obviousness.

Accordingly, claims 15, 17 and 23 are not rendered obvious from the combination of Sweatt, Hall-Jackson and Varga. Applicant respectfully requests the Examiner withdraw the rejection under 35 U.S.C. § 103(a).

CONCLUSION

In light of the foregoing, Applicants submit that claims 12, 14, 15 and 17-34 are in condition for allowance, and an early Notice of Allowance of all pending claims is respectfully requested.

In view of the above, Applicant believes the pending Application is in condition for allowance. Applicant believes this paper is being filed with all required fees. However, if any additional fee is due, including those for an extension of time please charge any fees required or credit any overpayment to Chalker Flores, LLP's Deposit Account No. 50-4863 during the pendency of this Application pursuant to 37 CFR 1.16 through 1.21 inclusive, and any other section in Title 37 of the Code of Federal Regulations that may regulate fees. If an extension of time is required with this response but is not included, Applicant hereby petitions for a Request for Extension of Time under 37 CFR 1.136(a).

If the Examiner has any questions or comments, or if further clarification is required, it is requested that the Examiner contact the undersigned at the telephone number listed below.

Dated: April 26, 2010

Respectfully submitted,

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